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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,034	02/21/2002	William Peter Van Antwerp	G&C 130.28-US-U1	6773

22462 7590 04/23/2003

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EXAMINER	
CHISM, BILLY D	

ART UNIT	PAPER NUMBER
1654	8

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,034	VAN ANTWERP ET AL.	
	Examiner	Art Unit	
	B. Dell Chism	1654	

-- Th MAILING DATE of this communication appears on the cov r sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is in response to Paper No. 6, filed 09 January 2003, wherein Applicants elected, with traverse, Group II, claims 15-26. Claims 1-14 and 27-32 have been withdrawn from consideration by the Examiner. Applicants assert that the Examiner failed to list Groups I and II as independent, thus, the restriction is improper. Consequently, the Applicants have improperly applied the MPEP §803 by stating that a proper restriction requires independent and distinct inventions for proper restriction. The Examiner would like to point out that this is not the case. MPEP§803 requires "independent OR distinct." For these reasons, the Examiner finds the Applicants' argument unpersuasive. The Applicants also assert that there is no burden on the Examiner to search the distinct inventions of Groups I and II. Although a search for one distinct invention could possibly yield some relevant art regarding the other distinct invention, and vice versa, the searches would no be co-extensive and would require additional and burdensome searches for the Examiner. Thus, the Applicants' argument is unpersuasive. The Applicants also assert that the distinct invention of Group I can only be made by the distinct inventive method of Group II, however, the Applicants are basing this argument on the fact that the final distinct invention of Group I is comprised of two separate components that renders the production of the distinct invention of Group I only possible via the distinct inventive methods of Group II. However, the distinct invention of Group I is a single composition comprising two different insulin species that form a heterodimeric complex and it is that heterodimeric complex which can be produced by methods other than those of distinct invention Group II. The Examiner again indicates that the Groups I and II are distinct for the reasons indicated in the

Restriction, Paper No. 5 filed 23 December 2002. The restriction is deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims15-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. It is suggested that independent claims 15 and 21 be fully expanded upon so as to clearly recite a complete preparation method including all the essential steps necessary for making the enabled insulin heterodimeric complex composition as instantly disclosed.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under 35 U.S.C. 112, second paragraph for the reasons set forth above.

4. Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: specific functionalities to be involved in the combining of the two insulin species, reactionary conditions for proper reactivity for the complex formation or non-formation.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-16, 20-22 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making compositions comprising human insulin/LISPRO heterodimeric complexes, does not reasonably provide enablement for methods of making any and/or all compositions comprising a heterodimeric complex of human insulin and any insulin variant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman,

230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to methods of stabilizing insulin formulations comprising combining two species of insulin to form a heterodimeric complex wherein the claims require a variant that the specification describes as being an insulin analog.

The state of the prior art and the predictability or lack thereof in the art: The art does not teach predictability or unpredictability of stability or the expectation of stability for dimers of insulin or insulin variants. In fact, as is disclosed in the specification, the effectiveness of insulin and insulin analogs for the stated purpose is limited due to aggregation. The specification (page 2 lines 23-26) also states that aggregation accounts for reduced reproducible delivery of effective therapeutic doses of the monomeric analog.

The amount of direction or guidance present and the presence or absence of working examples: Given the lack of teachings of predictability and unpredictability regarding the stability of insulin/insulin variant compositions, detailed teachings are required to be present in the disclosure to enable the skilled artisan to make and use polypeptides corresponding to a stable human insulin/insulin variant composition. Such teachings are absent. The specification discloses the method of stabilizing a human insulin/LISPRO combination, however, there is no disclosure of any other methods for producing a stabilized human insulin/insulin variant.

The breadth of the claims and the quantity of experimentation needed: Given the lack of teachings of predictability or unpredictability in the art regarding the variability in the stability of just any human insulin/insulin variant composition and in the absence of sufficient disclosure in applicant's specification to overcome the lack of teachings of predictability and/or unpredictability in the art, it would require undue experimentation by one of skill in the art to be able to make and use the invention commensurate in scope with the claims other than those drawn to human insulin/LISPRO heterodimeric complexes.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15 and 21 rejected under 35 U.S.C. 102(b) as being anticipated by Hansen *et al.* 1992 (US 5,149,777; PTO-1449, Paper No. 7, filed 28 January 2003) or by Balschmidt *et al.* 1998 (EP 0 837 072 A2; PTO-1449, Paper No. 7, filed 28 January 2003). Although difficult to interpret due to the U.S.C. 112, second paragraph rejection above, a method of making an insulin composition via combining a first and second insulin species is apparently claimed.

Hansen et al. and Balschmidt et al. each teach compositions comprising two or more human insulin species (analogs) which are combined therein (see, e.g., Hansen et al: col 10, lines 59-68 and claim 14; Balschmidt et al: page 8, lines 20-58). A heterodimeric complex would be inherent to such a combination of human insulin species (analogs) - especially since, as drafted,

the formation of a heterodimeric complex is not positively claimed as a step therein.

Therefore, each of the cited references is deemed to anticipate the instant claims above.

8. Art of Record

Mascarenhas 2003 (US 6514937 B1) teaches composition of two different insulin species (i.e., insulin growth factor/insulin growth factor binding protein-3) that complex for pharmaceutical use.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to B. Dell Chism whose telephone number is 703-306-5815. The examiner can normally be reached on 7:30 AM - 4:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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B. Dell Chism
17 April 2003

CHRISTOPHER R. TATE
PRIMARY EXAMINER